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Aryne Insertion Reactions Leading to Bioactive Fused Quinazolinones: Diastereoselective Total Synthesis of Cruciferane

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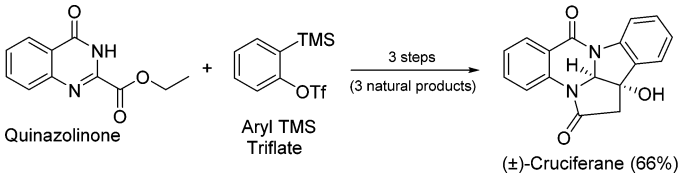
ABSTRACT



Insertion reactions of an in situ generated arynes to a variety of suitably substituted 1,3-quinazolin-4-ones have been demonstrated for a new efficient one-step approach to a diverse range of fused quinazolinone architectures. The present protocol has been effectively utilized to accomplish the concise total synthesis of recently isolated bioactive natural products tryptanthrin, phaitanthrins A–C, and cruciferane.

Quinazolinones are an important class of compounds and a building block for a large number of structurally diverse alkaloids with a wide range of biological activities.[1,2] More specifically, the fused quinazolinones such as asperlicins, benzomalvins, circumdatins, phaitanthrins, and their synthetic congeners have been imperative targets due to their structural architectures and promising bioactivities (Figure 1).[3] Several well-designed synthetic routes involving intramolecular cyclization strategies have been known for these significant targets.[3,4] After Kobayashi's discovery of a very mild way of generating highly reactive aryne intermediates,[5a] chemistry of arynes has become a subject of contemporary interest.[5] Since then, plenty of meticulous new applications of aryne reactions have been continuously reported by synthetic chemists.[6] On the basis of our continuing interest in the synthesis of quinazolinone alkaloids[7] and their retrosynthetic disconnections, we reasoned that the selective insertion of aryne between the 3-position nitrogen atom and suitable 2-position substituent of 1,3-quinazolin-4-ones would constitute an appropriate one-step new synthetic approach to the desired fused quinazolinone

(1) (a) Demeunynck, M.; Baussanne, I. *Curr. Med. Chem.* **2013**, *20*, 794. (b) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348. (c) Roy, A. D.; Subramanian, A.; Roy, R. *J. Org. Chem.* **2006**, *71*, 382. (d) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787 and references cited therein.

(2) (a) Amin, A. H.; Mehta, D. R.; Samarth, S. S. *Prog. Drug. Res.* **1970**, *14*, 218. (b) Johne, S. *Prog. Drug. Res.* **1982**, *26*, 259. (c) Johne, S. *Prog. Chem. Org. Nat. Prod.* **1984**, *46*, 159. (d) Sinha, S.; Srivastava, M. *Prog. Drug. Res.* **1994**, *43*, 143. (e) Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 11773. (f) Li, L.; Ge, J.; Wu, H.; Xu, Q.-H.; Yao, S. Q. *J. Am. Chem. Soc.* **2012**, *134*, 12157 and references cited therein.

(3) (a) Haynes, S. W.; Gao, X.; Tang, Y.; Walsh, C. T. *J. Am. Chem. Soc.* **2012**, *134*, 17444. (b) Zhichkin, P.; Kesicki, E.; Treiberg, J.; Bourdon, L.; Ronsheim, M.; Ooi, H. C.; White, S.; Judkins, A.; Fairfax, D. *Org. Lett.* **2007**, *9*, 1415. (c) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892. (d) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

(4) (a) Larraufie, M.-H.; Courillon, C.; Ollivier, C.; Lacôte, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, *132*, 4381. (b) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686. (c) Xiao, Z.; Yang, M. G.; Li, P.; Carter, P. H. *Org. Lett.* **2009**, *11*, 1421. (d) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027. (e) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (f) Snider, B. B.; Wu, X. *Org. Lett.* **2007**, *9*, 4913.

(5) (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211. (b) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (c) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (d) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (e) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (f) Chen, Y.; Larock, R. C. In *Modern Arylation Methods*; Ackerman, J., Ed.; Wiley/VCH: New York, 2009; pp 401–473. (g) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579 and references cited therein.

(6) (a) Hendrick, C. E.; McDonald, S. L.; Wang, Q. *Org. Lett.* **2013**, *15*, 3444. (b) Yun, S. Y.; Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 4668. (c) Goetz, A. E.; Garg, N. K. *Nature Chem.* **2013**, *5*, 54. (d) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208.

(7) Kshirsagar, U. A.; Argade, N. P. *Org. Lett.* **2010**, *12*, 3716.

10.1021/ol4018062

systems. We herein report our detailed studies on aryne-insertion reactions of quinazolinones and their applications in the synthesis of several natural and unnatural quinazolinone systems (Schemes 1−5 and Table 1).

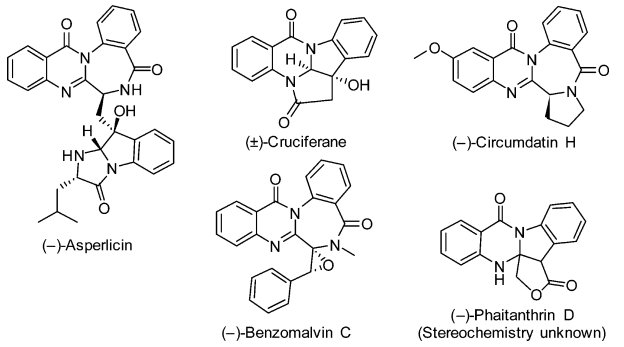
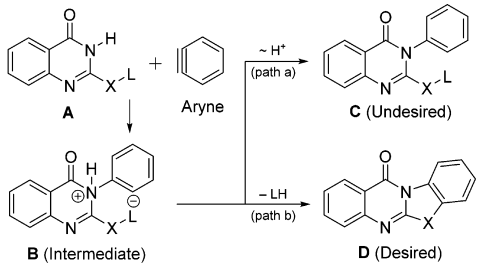


Figure 1. Bioactive fused quinazolinone and dihydroquinazolinone alkaloids.[1d,8]

Scheme 1. Synthetic Proposal for Aryne Insertion Reactions of 1,3-Quinazolin-4-ones

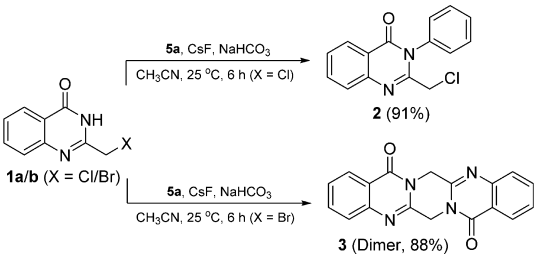


X = Broad range of substituents with electrophilic carbon unit; L = An appropriate leaving group.

As depicted in Scheme 1, our synthetic proposal for aryne insertion reactions of 1,3-quinazolin-4-ones was mainly based on the following fundamental concepts, namely: (i) the lone pair of electrons on the 3-position nitrogen atom in quinazolinone **A** would be sufficiently nucleophilic to regioselectively attack an in situ generated reactive arynes to afford a zwitterionic intermediate **B**; (ii) the intermediate **B** upon intramolecular prototropic shift would provide the undesired *N*-arylated product **C** via a strained four-membered transition state (path a); (iii) however, the intermediate **B** upon intramolecular cyclization with a displacement of suitable leaving group from 2-position of quinazolinone would lead to the desired aryl insertion product **D** via five/six/seven-membered transition states (path b); and (iv) tailoring the compatibility of carbanion

(8) (a) Tucker, A. M.; Grundt, P. *ARKIVOC* **2012**, *No. i*, 546. (b) Bergman, J.; Lindström, J.-O.; Tilstam, U. *Tetrahedron* **1985**, *41*, 2879. (c) Jao, C.-W.; Lin, W.-C.; Wu, Y.-T.; Wu, P.-L. *J. Nat. Prod.* **2008**, *71*, 1275. (d) Chen, M.; Gan, L.; Lin, S.; Wang, X.; Li, L.; Li, Y.; Zhu, C.; Wang, Y.; Jiang, B.; Jiang, J.; Yang, Y.; Shi, J. *J. Nat. Prod.* **2012**, *75*, 1167. (e) Danz, H.; Stoyanova, S.; Wippich, P.; Brattström, A.; Hamburger, M. *Planta Med.* **2001**, *67*, 411.

Scheme 2. Preliminary Studies on Aryne Insertion Reactions of 2-Halomethylquinazolinones



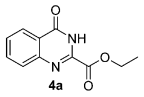
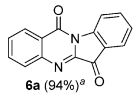
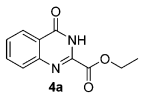
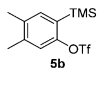
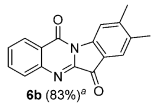
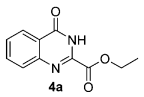
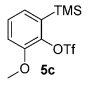
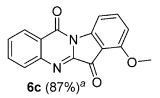
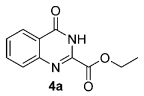
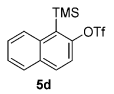
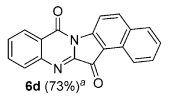
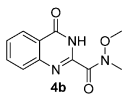
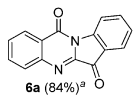
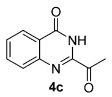
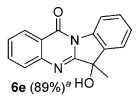
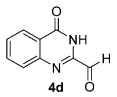
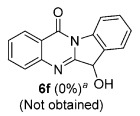
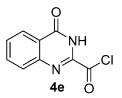
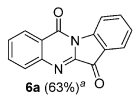
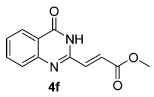
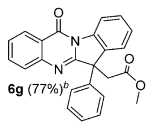
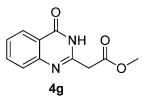
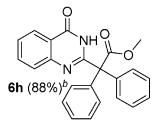
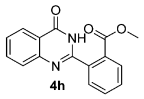
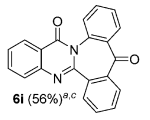
nucleophilicity with electrophilicity of 2-position carbon unit in an intermediate **B** for intramolecular cyclization would be feasible to make the reaction furnish desired aryne insertion product **D**.

The bioactive tryptanthrin (**6a**) has been isolated from numerous natural sources, and several synthesis of **6a** have been known.[8a,b] The fused quinazoline alkaloids tryptanthrin, phaitanthrins A−E and (±)-cruciferane, have been recently isolated from *Phaius mishmensis* and *Isatis tinctoria* (*Isatis indigotica* Fortune) and are potential antiviral and anticancer agents.[8c−e] We surmise that the tryptanthrin could be a biogenetic precursor of (±)-cruciferane. Exotic (±)-cruciferane is the first natural product with pyrroloindoloquinazoline skeleton and also encompasses an angular oxygen function alike antitumor antibiotics mitomycins.[9] On the basis of their structural features, we selected these as synthetic targets and instigated our studies on aryne insertion reactions of 1,3-quinazolin-4-ones. Initial aryne insertion reaction of 2-chloromethylquinazolinone **1a** with an in situ generated aryne intermediate exclusively furnished the corresponding *N*-arylated quinazolinone **2** in 91% yield (Scheme 2). The above experiment clearly indicated that the lone pair of electrons on 3-position nitrogen atom of quinazolinone is sufficiently nucleophilic to attack arynes under the present reaction conditions. However, reaction of 2-bromomethylquinazolinone **1b** with aryne was not possible, as the starting material **1b** underwent a self-coupling reaction to form the linear pentacyclic dimer **3**[10] in 88% yield via conjugative intermolecular-intramolecular nucleophilic substitution pathway.

Rewardingly, the insertion reaction of an in situ generated aryne from precursor **5a** to quinazolinone **4a** in acetonitrile at 25 °C was very clean and furnished the desired natural product tryptanthrin (**6a**) in 94% yield via *N*-arylation followed by a concomitant intramolecular cyclization route (Table 1, entry 1). As anticipated, the intermediate carbanion attacked on the proximal carbethoxy moiety to generate a new carbon−carbon bond prior to prototropic shift and exclusively delivered product **6a**. As described in Table 1, several requisite starting quinazolinones **4a**−**h** bearing suitable carbonyl units were prepared to study the generality of present approach.[11] Similarly, insertion reaction of symmetrical aryne from precursor **5b**

(9) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881.
(10) Gompper, R.; Breitschaft, W. *Angew. Chem.* **1983**, *95*, 727.

Table 1. Aryne Insertion Reactions of Quinazolinones[a,b]

entry	quinazolinone	aryl TMS triflate	product (% yield)
1	 **4a**	 **5a**	 **6a** (94%)[a]
2	 **4a**	 **5b**	 **6b** (83%)[a]
3	 **4a**	 **5c**	 **6c** (87%)[a]
4	 **4a**	 **5d**	 **6d** (73%)[a]
5	 **4b**	 **5a**	 **6a** (84%)[a]
6	 **4c**	 **5a**	 **6e** (89%)[a]
7	 **4d**	 **5a**	 **6f** (0%)[a] (Not obtained)
8	 **4e**	 **5a**	 **6a** (63%)[a]
9	 **4f**	 **5a**	 **6g** (77%)[b]
10	 **4g**	 **5a**	 **6h** (88%)[b]
11	 **4h**	 **5a**	 **6i** (56%)[a,c]

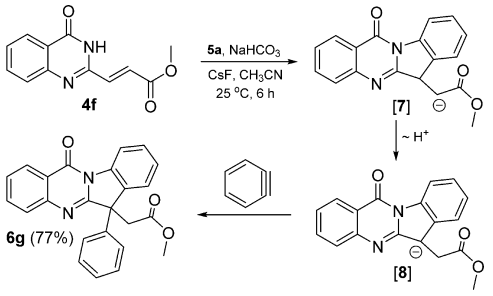
[a] Reaction conditions: quinazolinone (1.00 mmol), aryl triflate (1.20 mmol), CsF (2.40 mmol), $NaHCO_3$ (1.20 mmol), CH_3CN (10 mL), 25 °C, 6 h. [b] Reaction conditions: quinazolinone (1.00 mmol), aryl triflate (2.40 mmol), CsF (4.80 mmol), $NaHCO_3$ (2.40 mmol), CH_3CN (15 mL), 25 °C, 6 h. [c] The corresponding simple *N*-arylated product **6j** was also formed in 41% yield (Supporting Information).

to quinazolinone **4a** provided the desired product **6b** in 83% yield (Table 1, entry 2). Reaction of quinazolinone **4a** with unsymmetrical aryne from precursor **5c** was highly regioselective and exclusively formed the desired product **6c** in 87% yield (Table 1, entry 3). The lone pair of electrons on nitrogen atom in compound **4a** selectively attacked an electron deficient *meta*-position of aryne[12a] to form the product **6c**. Reaction of quinazolinone **4a** with yet another unsymmetrical aryne from precursor **5d** was also highly regioselective and exclusively delivered the desired product **6d** in 73% yield (Table 1, entry 4). The lone pair of electrons on nitrogen atom in compound **4a** selectively attacked a relatively electron deficient β-position carbon atom of α-naphthalyne to form the product **6d**. This observation is in accordance with literature precedence.[12b]

Reaction of quinazolinone **4b** with the Weinreb amide unit at the 2-position and symmetrical aryne from precursor **5a** also gave the desired product **6a** in 84% yield (Table 1, entry 5). Reaction of quinazolinone **4c** bearing an acyl unit at 2-position and symmetrical aryne from precursor **5a** yielded the desired cycloadduct **6e** in 89% yield (Table 1, entry 6). Reaction of quinazolinone **4d** bearing a formyl unit at 2-position with symmetrical aryne from precursor **5a** underwent excessive decomposition and failed to provide the desired product **6f** (Table 1, entry 7). Reaction of quinazolinone **4e** with an acid-chloride unit at 2-position and symmetrical aryne from precursor **5a** also afforded the desired product **6a** but only in 63% yield (Table 1, entry 8). The decline in yield could be due to relatively less stability of an acid chloride under the present reaction conditions.

Reaction of quinazolinone **4f** bearing the α,β-unsaturated unit at 2-position with symmetrical aryne from precursor **5a** (1.20/2.40 mmol) exclusively furnished the double aryne inclusion product **6g** in 35/77% yield (Table 1, entry 9). As depicted in Scheme 3, product **6g** was formed via *N*-arylation followed by a Michael addition to form the intermediate **7**, which on an in situ prototropic shift formed the more stable doubly conjugated carbanionic intermediate **8**. Intermediate **8** bearing net negative charge being relatively more reactive than the starting material **4f** itself undergoes second arylation process at a faster rate and forms product **6g** with a generation of new quaternary center. Reaction of quinazolinone **4g** with an active methylene unit ($-CH_2CO_2Me$) at the 2-position and symmetrical aryne from precursor **5a** (1.20/2.40 mmol) underwent stepwise double *C*-arylation

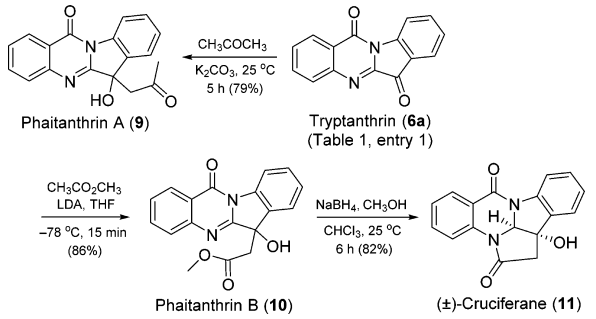
Scheme 3. Proposed Mechanism for Aryl Insertion and *C*-Arylation



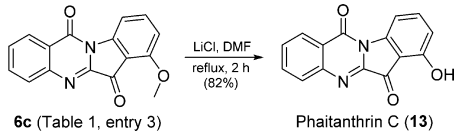
(11) (a) Kraus, G. A.; Guo, H. *J. Org. Chem.* **2009**, *74*, 5337. (b) Zhou, H. B.; Liu, G. S.; Yao, Z. J. *J. Org. Chem.* **2007**, *72*, 6270. (c) Bergman, J.; Brynolf, A. *Tetrahedron* **1990**, *46*, 1295.

(12) (a) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224. (b) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.

Scheme 4. Synthesis of Phaitanthrin A, Phaitanthrin B, and Cruciferane



Scheme 5. Synthesis of Phaitanthrin C



process and exclusively provided a new quaternary carbon bearing product **6h** in 39/88% yield (Table 1, entry 10). The monoarylated intermediate product exhibits higher enol character than the starting material **4g** and hence enhances the formation of diarylated product **6h**. Present observation is in accordance with a recent literature report by Mhaske and co-workers.[13] Finally, reaction of quinazolinone **4h** with symmetrical aryne from precursor **5a** afforded the desired seven membered product **6i** in 56% yield (Table 1, entry 11). The corresponding simple *N*-arylated product was also formed in 41% yield and it could be attributed to a slower rate of generation of seven membered ring systems utilizing the relatively less reactive aromatic ester unit.

In the next part of our study, the fused quinazolinone systems were used for the synthesis of recently isolated bioactive natural products (Scheme 4). K_2CO_3-induced chemoselective aldol condensation of acetone with natural product tryptanthrin (**6a**) gave the phaitanthrin A (**9**) in 79% yield.[8c] Several attempts to perform the Reformatsky reaction on tryptanthrin (**6a**) were unsuccessful. However, chemoselective condensation of tryptanthrin (**6a**) with methyl acetate using LDA as the base at −78 °C was successful and provided the desired natural product phaitanthrin B (**10**) in 86% yield. The sodium borohydride induced hydroxyl directed[14] highly chemo- and diastereoselective reductive intramolecular cyclization of phaitanthrin B (**10**) furnished yet another natural product (±)-cruciferane (**11**) in 82% yield. As indicated in the

(13) Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *Org. Lett.* **2012**, *14*, 3994.

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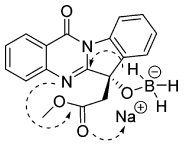

Figure 2. Proposed TS for reductive intramolecular cyclization.

transition state **12** from Figure 2, initially the boron atom forms a complex with an adjacent oxygen atom and delivers a hydride from the same phase to imine moiety to generate nitrogen anion in the opposite phase, which undergoes concomitant intramolecular cyclization to form a γ-lactam unit. We feel that the present selective intramolecular cyclization follows a concerted pathway, and it is a both enthalpically (formation of amide bond) and entropically (formation of five-membered ring) favored process. The demethylation of quinazolinone **6c** using BBr_3/BCl_3 was not very efficient and product **13** was obtained only in 15% yield. Finally, LiCl-induced demethylation of quinazolinone **6c** in refluxing DMF afforded the desired natural product phaitanthrin C (**13**) in 82% yield (Scheme 5). The analytical and spectral data obtained for natural products tryptanthrin, phaitanthrins A−C and cruciferane were in complete agreement with the reported data.[8c,d]

In summary, we have demonstrated a new simple and efficient one-step aryne-based synthetic protocol for a diverse range of fused quinazolinones. It has also been successfully utilized to accomplish a concise total synthesis of five recently isolated different bioactive quinazolinone based natural products. More specifically, the first total synthesis of (±)-cruciferane has been accomplished in three steps with 66% overall yield via two natural products as the intermediates. In the synthesis of cruciferane, selective reduction of an imine moiety in the quinazolinone unit in the presence of an aliphatic ester moiety is noteworthy from a basic chemistry point of view. The present transition metal free convergent approach to fused quinazolinones is general in nature and will be useful to design several focused minilibraries of natural and unnatural quinazolinone systems for SAR studies.

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Supporting Information Available. Experimental procedures, tabulated analytical and spectral data of compounds **2**, **3**, **4b**, **4f**, **6a**−**e**, **6g**−**j**, **9**−**11**, and **13**. ^{1}H NMR, ^{13}C NMR, and DEPT spectra of compounds **3**, **4f**, **6a**−**e**, **g**−**j**, **9**−**11**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.